REMARKS

Claims 2-9, 11, and 22-25 are pending in the instant application. In view of the following remarks, reconsideration of the application is respectfully requested.

Declaration

The Examiner has maintained the rejection of claims 2-9, 11, and 22-25 under 35 U.S.C. § 103(a) as allegedly unpatentable over Ferrara *et al.* (US 6,455,283 B1), alone (claims 2-5, 7-9, 11, 22, 23 and 25) or in further view of Bentz *et al.* (EP 0 512 844 A1) (claims 6 and 24). In maintaining the rejection, the Examiner asserts that the Declaration of Stephen Jaspers under 37 C.F.R. § 1.132 ("Jaspers Declaration") "is insufficient to overcome the above mentioned prior art rejections set forth in the last Office action because: the declaration is largely opinion/argument only, and presents no further supporting evidence." (Office Action dated 1/25/2008 ["Office Action"] at page 2.)

Applicants disagree with the Examiner's statement above as a basis for maintaining the present rejection under § 103. First, to the extent that the Jaspers Declaration presents opinion testimony of an expert in the pertinent art, setting forth statements of fact relevant to an inquiry under § 103, such testimony is entitled to consideration and must be given weight. (*See* MPEP § 716.01(c)(III).) As further discussed hereinbelow, when this testimony is considered in light of other evidence provided with the Declaration, such expert testimony shows non-obviousness of the present invention.

Second, Applicants note that in addition to opinion testimony, the Jaspers Declaration does indeed present further, objective evidence supporting a showing of non-obviousness. In particular, the Jaspers Declaration sets forth specific facts regarding PDGF family members, both those members known as of the effective filing date of the application, as well as PDGF-C (to which the present claims are directed). (*See* Jaspers Declaration at ¶¶ 11-13.) These facts include information on (1) how PDGF-C protein structure impacts biological activity as well as (2) the fact that this structure was unique, *i.e.*, no other known PDGF family member exhibited a similar two-domain structure. (*See id.*) These statements of fact are supported by citation to, and the submission of,

scientific references (Li *et al.*, *Nature Cell Biol.* 2:302-309, 2000; Fredriksson *et al.*, *J. Biol. Chem.* 280:26856-26862), further demonstrating the objective nature of this evidence.

Moreover, as discussed in the Jaspers Declaration, and based on the cited references, a variety of PDGF-C truncations would be inadequate to generate active fragments of the molecule, while a PDGF-C polypeptide as recited in the present claims does indeed correspond to a bioactive fragment. As further discussed below, this evidence is pertinent to non-obviousness of the present claims, since (1) it demonstrates an unexpected result for the recited polypeptide (namely, bioactivity relative to other fragments comprising the same domain); and (2) it further indicates that, at least in the context of the PDGF-C molecule, identification of a bioactive fragment was not a routine matter.

Sufficiency of the Jaspers Declaration with regard to a showing of non-obviousness is further addressed in Applicants' response to the 103 rejections, below.

Rejections under 35 U.S.C. § 103

A. Ferrara

The Examiner has maintained the rejection of claims 2-5, 7-9, 11, 22, 23 and 25 under 35 U.S.C. § 103(a) as allegedly unpatentable over Ferrara *et al.* (US 6,455,283 B1). Specifically, the Examiner states, *inter alia*, that the TSM test is "merely one of several criteria [that] may be used for analyzing obviousness [under § 103]" and asserts that "determining the structural-functional relationship of a newly discovered polypeptide, and making functional fragments thereof are both desirable and routine in the art." (Office Action at page 4.) The Examiner further alleges that "such determination for a known polypeptide and achieving functional fragments thereof does not constitute novel inventive concept, given the fact that Ferrara has taught both the amino acid sequence and the functional property of the polypeptide." (*Id.* at page 4, bridging to page 5.)

The Examiner goes on to assert that Applicants' arguments regarding the unique structure of PDGF-C protein, including the inadequacy of partial N-terminal

deletions to generate active fragments, are "not persuasive" for reasons set forth with respect to the Jaspers Declaration. In this regard, Applicants note that the Examiner's specific reasons as set forth in regard to the Jaspers Declaration are essentially the same as summarized above with respect to making functional fragments. In particular, in response to the Jaspers Declaration, the Examiner states, *inter alia*, that "although Ferrara does not teach or suggest the recited fragment or the approximate boundaries of the growth factor domain, it is less relevant as mapping out a functional fragment or defining the structural-functional relationship of a newly discovered protein was both desirable and routine in the art at the time the present invention was filed." (Office Action at page 3.)

The Examiner further states that "whether the polypeptide has a two-domain structure are irrelevant to the *claimed* invention," and that "what is relevant is the claimed functional fragments." (Office Action at page 5.) In this respect, the Examiner again relies on the allegation that "it is routine in the art to determine the structural-functional relationship of a polypeptide, and to make functional fragments thereof." (*Id.*)

Applicants maintain traversal of the instant rejection, for reasons of record as well as the reasons set forth hereinbelow. In particular, the instant rejection under 35 U.S.C. § 103 is improper for at least three reasons. First, the Examiner attempts to establish certain facts – namely, the allegation that defining the structural-functional relationship of a newly discovered protein was "routine in the art at the time the present invention was filed" – without supporting documentary evidence. Second, the Examiner's reasons essentially rely on an "obvious to try" rationale, which, under *KSR International Co. v. Teleflex Inc.* and the PTO's own *Guidelines for Determining Obviousness under KSR*, is improper absent a proper finding that there are "a finite number of identified, predictable potential solutions" to the problem at hand. Third, even assuming, *arguendo*, a *prima facie* case of obviousness, Applicants have presented objective evidence (namely, Li *et al.* and Fredriksson *et al.*, as cited in the Jaspers Declaration) establishing that a fragment of PDGF-C as claimed is unexpectedly superior in bioactivity to other fragments having partial N-terminal deletions. These reasons are further set forth below.

1. The Examiner's Rejection Relies on Alleged Facts that are Unsupported by Any Documentary Evidence

In setting forth the instant rejection under 35 U.S.C. § 103, the Examiner repeatedly asserts that "defining the structural-functional relationship of a newly discovered protein was ... routine in the art at the time the present invention was filed." (Office Action at page 3, 1st full paragraph; *see also id.* at page 4, bottom, and page 5, bottom.) The Examiner makes these assertions, however, without reference to any documentary support in the record. Thus, the Examiner attempts to take official notice of certain facts underlying the alleged basis for the instant rejection.

According to the MPEP and relevant case law, official notice unsupported by documentary evidence "should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art[,] are capable of *instant and unquestionable demonstration* as being well-known." MPEP § 2144.03(A) (emphasis provided). *See also In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970) (stating that notice facts beyond the record which may be taken by the examiner ***must be "capable of such instant and unquestionable demonstration as to defy dispute"***). Further, it is particularly improper to take official notice of the state of the art. *See In re Eynde*, 480 F.2d 1364, 1370, 178 USPQ 470, 474 (CCPA 1973); *see also* MPEP § 2144.03(A). In *Eynde*, the court stated as follows:

> [W]e reject the notion that judicial or administrative notice may be taken of the state of the art. The facts constituting the state of the art are normally subject to the possibility of rational disagreement among reasonable men and are not amenable to the taking of such notice.

Eynde, 480 F.2d at 1370. Moreover, general conclusions concerning what is common knowledge to one of ordinary skill in the art, without specific factual findings and some concrete evidence in the record to support these findings, will not support an obviousness rejection. *See In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001); MPEP § 2144.03(B).

In the instant case, the Examiner's assertion that – "defining the structural-functional relationship of a newly discovered protein was ... routine in the art at the time the present invention was filed" – is not "capable of such instant

and unquestionable demonstration as to defy dispute." Rather, the Examiner's statement goes directly to characterizing the state of the art, normally subject to rational disagreement, and thus "not amenable to the taking of such notice." *See Eynde*, 480 F.2d at 1370; MPEP § 2144.03(A).

Indeed, the objective evidence of record suggests that, in the instant case, determining the structural-functional relationship of the PDGF-C protein was not routine. For example, Fredriksson *et al.*, previously submitted as supporting Exhibit C of the Jaspers Declaration, shows that even truncated variants of PDGF-C that lack the CUB domain, but retain a significant portion of the hinge region, are inactive (*see* Fredriksson *et al.*, *J. Biol. Chem.* 280:26856-26862, 2005, p. 26859, Figure 2.) Applicants note that Fredriksson *et al.* has a publication date seven years after Ferrara's earliest claimed filing date of March, 1998. This seven year period – from Ferrara until publication in the scientific literature of Fredriksson's studies pertaining to PDGF-C structure and bioactivity – do ***not*** support the Examiner's assertion that "defining the structural-functional relationship of a newly discovered protein was ... routine in the art at the time the present invention was filed."

Accordingly, Applicants respectfully request that the Examiner provide documentary evidence of the assertion that "determining the structural-functional relationship of a newly discovered protein was routine." If the Examiner is relying on personal knowledge to support this contention, then Applicants request that the Examiner provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. *See* MPEP § 2144.03(C); 37 C.F.R. § 1.104(d)(2). If such documentary evidence is not provided, then the instant rejection under 35 U.S.C. § 103 cannot be maintained, and withdrawal of the instant rejection is respectfully requested.

2. The Examiner's Rejection Relies on an "Obvious to Try" Rationale that is not Supported by the Evidence of Record

Applicants note that the Examiner cites to *KSR International v. Teleflex, Inc.* for the position that a *prima facie* showing under a TSM analysis is not required for a rejection under § 103, and instead relies on an allegation that once the amino acid

sequence and a function for a given protein are known in the art, it would be "desirable and routine" for one of skill in the art to determine the structural-functional relationship of the protein. (*See* Office Action at page 4.) Thus, the Examiner appears to accept that there is no *prima facie* case of obviousness under a TSM analysis, but instead relies on an "obvious to try" rationale. This rationale for the rejecting the instant claims is not supported by the evidence of record.

First, with regard to the legal and administrative standards for applying an "obvious to try" rationale under *KSR*, the Supreme Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR International v. Teleflex, Inc.*, 127 S.Ct. 1727, 1742, 82 USPQ2d 1385 (2007). In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." (*Id.*)

Such is not the case here. In particular, rather that show a "finite number of identified, predictable solutions" with regard to active fragments of PDGF-C, the closest art of record, Ferrara, only states that "VEGF-E [PDGF-C] polypeptide variants include, for instance, VEGF-E polypeptides wherein one or more amino acid residues are added, deleted, or substituted at the N- or C-terminus of the [full-length VEGF-E sequence ("Ferrara's SEQ ID NO:2")] or within the sequence as well as active fragments thereof." (Ferrara at col. 8, ll. 15-24.) Ferrara does not teach or suggest any particular active fragments of PDGF-C, nor does Ferrara otherwise provide any specific guidance as to which fragments of PDGF-C would be active. (Jaspers Declaration at ¶ 19.) Ferrara fails to teach the approximate boundaries of the growth factor domain of Ferrara's SEQ ID NO:2, nor does Ferrara disclose or suggest that proteolytic cleavage of an N-terminal region, comprising the CUB domain, releases the active growth factor domain from the full-length protein. (Jaspers Declaration at ¶ 19.) Thus, Ferrara merely refers to "active fragments" of PDGF-C in the most general sense, without identifying any particular regions of the protein that might confer, inhibit, or otherwise impact PDGF-C bioactivity.

Indeed, the evidence as presented in the Jaspers Declaration, and its supporting Exhibits B and C, underscores the insufficiency of Ferrara's disclosure. In this regard – and in response to the Examiner's assertions dismissing, as allegedly

"irrelevant," the Jaspers Declaration's statements with respect to the unique domain structure of PDGF-C – the Jaspers Declaration establishes that the unique domain structure of PDGF-C has particular significance with respect to activation. (*See* Jaspers Declaration at ¶ 21.) As noted in the Jaspers Declaration, the PDGF-C protein is active only upon cleavage of the CUB domain from the growth factor domain (*id.* at ¶ 13, citing Li *et al.*), and even truncated variants of PDGF-C that lack the CUB domain, but retain a significant portion of the hinge region, are inactive (Jaspers Declaration at ¶ 13, citing Fredriksson *et al.*). Thus, this unique domain structure, of PDGF-C protein, particularly in the absence in the art of other PDGFs having these characteristics (*see* Jaspers Declaration at ¶¶ 11, 21), suggests that identification of active fragments of PDGF-C would not have been predictable as the time of the present invention.

Accordingly, the present case fails to present the type of situation contemplated by the Supreme Court when it stated that an invention may be deemed obvious if it was "obvious to try." Indeed, consistent with the Supreme Court's KSR decision, the PTO's own Examination Guidelines specifically require that, to reject a claim as allegedly "obvious to try," the Examiner must articulate, *inter alia*, "a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem." *Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc.*, Fed. Reg. Vol. 72, No. 195, October 10, 2007, page 57532. For at least the reasons above, the Examiner has not articulated such a finding.

Therefore, for at least the reasons above, and in addition to the reasons previously discussed, the present rejection under 35 U.S.C. § 103 is improper. Withdrawal of the rejection is therefore respectfully requested.

3. Non-obviousness of the Claimed PDGF-C Polypeptide is Further Demonstrated by Unexpected Results

Even assuming, for argument's sake only, a *prima facie* case of obviousness, Applicants have presented objective evidence showing unexpected results achieved with a PDGF-C polypeptide corresponding to a PDGF-C polypeptide as recited in the present claims. According to the Federal Circuit, the ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of

the evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. *See In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); MPEP § 716.01(d). Therefore, even if a *prima facie* case is established under 35 U.S.C. § 103, if applicant produces rebuttal evidence of adequate weight, "the holding of *prima facie* obviousness, being but a legal inference from previously uncontradicted evidence, is dissipated." *In re Piasecki*, 745 F.2d 1468, 223 USPQ 785, 788 (Fed. Cir. 1984). In this respect, unexpected results of the claimed invention are objective evidence "relevant to the issue of obviousness and must be considered in every case in which they are present." MPEP § 2141.

In the instant case, the objective evidence of record shows that a fragment of PDGF-C corresponding to a polypeptide as presently claimed is unexpectedly superior in bioactivity to a full-length PDGF-C polypeptide as well as other fragments having partial N-terminal deletions. As discussed in the Jaspers Declaration, the PDGF-C growth factor domain by itself, in the absence of the CUB domain, is active as a high affinity agonist for PDGF receptor α ("PDGFRα"), while the full-length PDGF-C protein is not. (Jaspers Declaration at ¶ 13.) In standard mitogenesis assays, PDGF-C is active only upon cleavage of the CUB domain from the growth factor domain (core PDGF) domain, as demonstrated, for example, by studies described in Li *et al.*, *Nature Cell Biol.* 2:302-309, 2000 (*see, e.g.*, p. 303 [1st col., 2nd para.] to p. 305 [1st col., top] and Figure 3). Partial deletion of the N-terminus is inadequate generate an active fragment of PDGF-C, as shown by studies described by Fredriksson *et al.*, *J. Biol. Chem.* 280:26856-26862, 2005. As demonstrated by Fredricksson *et al.*, even truncated variants of PDGF-C that lack the CUB domain, but retain a significant portion of the hinge region, are inactive (*see* Fredriksson *et al.* at, *e.g.*, p. 26859, Figure 2). (Jaspers Declaration at ¶ 13.)

The superior activity of a fragment of PDGF-C having the growth factor domain, but lacking the CUB domain and a significant portion of the hinge region, could not have been predicted by an ordinarily skilled artisan on the basis of the prior art of record. As noted in Applicants' previous response, Ferrara does not specifically teach or suggest a unique, two-domain structure for PDGF-C containing an active growth factor domain. (Jaspers Declaration at ¶ 19.) In particular, Ferrara does not teach the approximate boundaries of the growth factor domain of Ferrara's SEQ ID NO:2, nor does

Ferrara disclose or suggest that proteolytic cleavage from the inactive precursor of an N-terminal region, comprising the CUB domain and a significant portion of the hinge region, releases the active growth factor domain from the full-length protein. (*Id.*) Furthermore, as noted in Applicants' previous response, a polypeptide chain as recited in the instant claims 11 and 22 (a polypeptide chain "consisting of residues X-345 of SEQ ID NO:2, wherein X is an integer from 226 to 235, inclusive") corresponds to bioactive fragment of PDGF-C having the growth factor domain, but lacking the CUB domain and a significant portion of the hinge region. (*Id.* at ¶ 14.) Accordingly, the studies of Fredrikkson *et al.* as summarized above are evidence of unexpected results showing non-obviousness of the claimed invention.

For at least the reasons above, the present claims are patentable over Ferrara under 35 U.S.C. § 103. Withdrawal of the rejection is therefore, again, respectfully requested.

B. Ferrara in view of Bentz

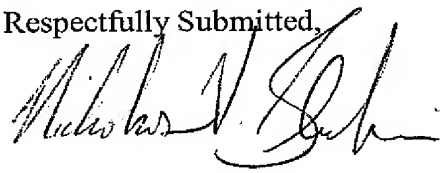
The Examiner has maintained the rejection of claims 6 and 24 under 35 U.S.C. § 103(a) as allegedly unpatentable over Ferrara, as applied to claims 2-5, 7-9, 11, 22, 23 and 25, and further in view of Bentz *et al.* (EP 0 512 844 A1).

Applicants maintain traversal of the instant rejection. For the reasons set forth above as well as reasons previously of record, the present claims are patentable over Ferrara. Bentz *et al.* do not cure the deficiencies of Ferrara. Accordingly, claims 6 and 24, which depend directly from claims 11 and 22, are also patentable over the cited art. Withdrawal of the rejection is therefore respectfully requested.

CONCLUSION

On the basis of the above remarks, Applicants believe that each rejection has been addressed and overcome. Reconsideration of the application and its allowance are requested. If for any reason the Examiner feels that a telephone conference would expedite prosecution of the application, the Examiner is invited to telephone the undersigned at (206) 442-6558.

Respectfully Submitted,



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